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ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

Hodgkin lymphoma: 2025 update on diagnosis, risk-stratification, and management

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Abstract

Disease Overview: Hodgkin lymphoma (HL) is an uncommon B-cell lymphoid malignancy affecting 8570 new patients annually and representing ~10% of all lymphomas in the United States.

Diagnosis: HL is composed of two distinct disease entities: classical HL and nodular lymphocyte predominant HL (also called nodular lymphocyte predominant B-cell lymphoma). Nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich HL are subgroups of classical HL.

Risk Stratification: An accurate assessment of the stage of disease in patients with HL is critical for the selection of the appropriate therapy. Prognostic models that identify patients at low or high risk for recurrence, as well as the response to therapy as determined by positron emission tomography (PET) scan, are used to optimize therapy.

Risk-Adapted Therapy: Initial therapy for HL patients is based on the histology of the disease, the anatomical stage and the presence of poor prognostic features. Patients with early-stage disease are typically treated with combined modality strategies utilizing abbreviated courses of combination chemotherapy followed by involved-field radiation therapy, whereas those with advanced stage disease receive a longer course of chemotherapy often without radiation therapy. However, newer agents including brentuximab vedotin and anti-PD-1 antibodies are now standardly incorporated into frontline therapy.

Management of Relapsed/Refractory Disease: High-dose chemotherapy (HDCT) followed by an autologous stem cell transplant (ASCT) is the standard of care for most patients who relapse following initial therapy. For patients who fail HDCT with ASCT, brentuximab vedotin, PD-1 blockade, non-myeloablative allogeneic transplant or participation in a clinical trial should be considered.

1 | DISEASE OVERVIEW

Hodgkin lymphoma (HL) affects ~8570 new patients in the United States each year.[1] The disease has a bimodal distribution with an increased incidence in young adults and in patients 55 years and older.[2,3] There are no clearly defined risk factors for the development of this disease and the cause of HL remains unknown. Factors shown to be associated with HL include familial factors, viral exposures and immune suppression.[2,4] Same sex siblings of patients with HL have a 10-fold higher risk for developing the disease,[5–7] and a monozygotic twin of a patient with HL has a significantly increased risk of developing HL when compared with a dizygotic twin sibling of a patient with HL.[8,9] Although these familial factors may suggest a genetic cause for this disease, research also suggests that an abnormal immune

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response to infection may play a role in the pathogenesis of HL. Epidemiologic and serologic studies have implicated Epstein–Barr virus (EBV) in the etiology of HL and the EBV genome was been detected in tumor specimens from patients with HL.[10] Other childhood infectious illnesses including chickenpox, measles, mumps, rubella, and pertussis, however, are negatively associated with the risk of HL and are possibly protective.[11] There is also an association with human immunodeficiency (HIV) infection, in that HIV infected patients have a significantly increased risk of HL when compared with the general population.[12] Overall, HL in immunosuppressed patients, including those who are HIV positive, is associated with advanced stage of disease at presentation, unusual sites of disease, and a poorer outcome after initial therapy.[13,14]

Over the past 4 decades, advances in radiation therapy, the development of combination chemotherapy regimens, and the addition of antibody drug conjugates and immune checkpoint inhibitors have significantly increased the cure rate of patients with HL. Currently, more than 80% of all newly diagnosed patients younger than 60 years are likely to be cured of their disease.

2 | DIAGNOSIS

At the time of diagnosis, the majority of patients with HL present with supradiaphragmatic lymphadenopathy. Patients commonly present with cervical, anterior mediastinal, supraclavicular, and axillary lymph node involvement, while the inguinal areas are less frequently involved. Approximately one third of patients present with systemic symptoms that include fever, night sweats, and weight loss; and many patients also present with chronic pruritis. While the disease most commonly involves contiguous lymph node groups, HL may also affect extranodal tissues by direct invasion or by hematogenous spread. The most commonly involved extranodal sites are the spleen, lungs, liver, and bone marrow.

The initial diagnosis of HL can only be made by a biopsy. Fine needle aspiration or core needle biopsies are inadequate because the architecture of the lymph node is extremely important for an accurate diagnosis. HL is a unique malignancy in that the tumor cells constitute the minority of the cellular population and an inadequate biopsy may fail to include malignant cells in the specimen.[15] To confirm the diagnosis, it is necessary to identify the malignant Reed-Sternberg cell, which is of follicular center B-cell origin,[16,17] within the appropriate cellular environment of normal reactive lymphocytes, eosinophils and histiocytes. Based on the World Health Organization Classification of Hematolymphoid Tumors, HL is composed of two distinct disease entities; the more commonly diagnosed classical HL and the rare nodular lymphocyte predominant HL.[18] Nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich HL are subgroups under the designation of classical HL. However, the Clinical Advisory Committee associated with the International Consensus Classification of Mature Lymphoid Neoplasms recently concluded that new terminology is warranted for nodular lymphocyte predominant Hodgkin lymphoma, based on major biological and clinical differences with classical Hodgkin lymphoma and the close relationship with T-cell/histiocyte-rich large B-cell lymphoma.[19] The term nodular lymphocyte predominant B-cell lymphoma (NLPBL) was introduced.[20] It remains to be seen if this will be generally accepted.

2.1 | Classical Hodgkin lymphoma

The presence of malignant multinucleated giant Reed-Sternberg cells within the characteristic reactive cellular background is the pathologic hallmark of classical HL. Painless lymphadenopathy is the most common clinical manifestation of classical HL, although each histological subtype has its own unique clinical features.[21] Nodular sclerosis, the most common subtype, tends to effect adolescent and young adults more commonly and usually presents with localized disease involving cervical, supraclavicular and mediastinal regions. Mixed cellularity HL is more prevalent in the pediatric, as well as older age groups, and is commonly associated with a more advanced stage of disease and a poorer prognosis. The incidence of lymphocyte depletion HL appears much lower than previously reported, with many of these cases reclassified as non-Hodgkin lymphoma. This subtype occurs mainly in older age patients and in patients with acquired immune deficiency syndrome. These patients typically present with symptomatic extensive disease without peripheral lymphadenopathy. Lymphocyte rich classical HL represents a subtype similar to nodular lymphocyte predominant HL (see below) on morphologic grounds; however, the Reed-Sternberg cells have a more classical immunophenotype consistent with classical HL.

Prior research showed overexpression of programmed death-1 (PD-1) ligands, including PD-L1 (CD274/B7-H1) and PD-L2 (CD273/B7-DC), on Reed-Sternberg cells.[22,23] Copy number variation and genetic alterations at chromosome 9p24.1, as well as increased JAK2 signaling, account for the majority of cases with overexpression of PD-L1 and PD-L2.[22] PD-L1/PD-L2 alterations are a defining feature of Hodgkin lymphoma and result in very high expression of PD-L1 or PD-L2 on the cell surface, thereby protecting Reed-Sternberg cells from T-cell mediated killing. While amplification of 9p24.1 is more common in patients with advanced stage disease and is associated with shorter progression-free survival in patients treated with chemotherapy, PD-L1 expression and MHC class II positivity on Reed-Sternberg cells are predictors of a favorable outcome after PD-1 blockade.[23]

Recent profiling of circulating tumor DNA levels has revealed two distinct classical HL genomic subtypes (cluster H1 and H2) with characteristic clinical and prognostic correlates, as well as distinct transcriptional and immunological profiles.[24] Cluster H1 tumors, seen more commonly in younger patients, comprised approximately 68% of cases and were dominated by somatic mutations in genes canonically involved in NFkB, JAK/STAT, and PI3K signaling pathways. Conversely, cluster H2 tumors, which comprised ~32% of cases and were associated with an inferior outcome, were primarily characterized by various SCNA events and mutations in *TP53* and *KMT2D*.

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2.2 | Nodular lymphocyte predominant Hodgkin lymphoma

Nodular lymphocyte predominant HL, or nodular lymphocyte predominant B-cell lymphoma as recently proposed,[20] constitutes a unique clinical pathologic entity that is significantly different to classical HL. Pathologically, lymphocyte predominant HL lacks the typical Reed-Sternberg cells, and instead is characterized by a neoplastic population of larger cells with folded lobulated nuclei known as lymphocytic and histiocytic (L&H) cells. Unlike classical HL, these cells are CD20+ and commonly negative for CD30.[25] Lymphocyte predominant HL is more frequently seen in men and constitutional symptoms at presentation as well as extranodal disease are rare. Patients usually present with limited nodal disease that classically affects the neck region and spares the mediastinum. The natural history of lymphocyte predominant HL differs from classical HL in that it has an indolent course with a tendency for late recurrences.[26]

3 | RISK STRATIFICATION

An accurate assessment of the stage of disease in patients with HL is critical for the selection of the appropriate therapy. The staging system for patients with HL is based on whether the involved lymph nodes are on one or both sides of the diaphragm, the number of involved sites, whether the sites of involvement are bulky, whether there is contiguous extranodal involvement or disseminated extranodal disease, and whether typical systemic symptoms (B symptoms) are present. Fluorodeoxyglucose positive emission tomography (FDG-PET) scanning has emerged as an important tool in the staging of patients with HL in that it significantly adds to the staging information obtained using other standard radiographic methods.[27,28]

Many patients with HL can be cured with standard treatment and are therefore at risk for potential long-term complications. Factors that identify patients at low or high risk for recurrence would therefore be most useful in optimizing therapy based on the patient's expected clinical outcome, to avoid over-treatment of some patients and under-treatment of others. Prognostic factors for early-stage HL have been identified and include the presence of a large mediastinal mass, an elevated sedimentation rate, involvement of multiple nodal sites, extranodal involvement, age ≥50 years, or massive splenic disease.[29]

In contrast, in patients with advanced HL, disease bulk and other traditional prognostic variables have been found to be less predictive of outcome. A different prognostic scoring system was therefore developed for these patients by the International Prognostic Factor Project on advanced HL.[30] This study identified seven variables (age ≥45 years, presence of stage IV disease, male sex, white blood count ≥15 000 cells/μL, lymphocyte count <600 cells/μL, albumin <4.0 g/dL, and hemoglobin <10.5 g/dL) that predicted patient outcome in a multivariate analysis. Patients with five or more factors were found to have a 5-year freedom from progression of 42%, whereas patients with no negative prognostic factors had an 84% likelihood of being free from progression at 5 years. However, as outlined below, the FDG-PET results during or after frontline treatment may have greater prognostic significance that the abovementioned pretreatment risk stratification.[31–33] Furthermore, metabolic tumor volume (MTV), as determined on the baseline FDG-PET scan, improves risk stratification of patients with HL and is a predictive factor of response to frontline combination chemotherapy regimens.[34,35]

For patients with nodular lymphocyte-predominant HL, the lymphocyte-predominant international prognostic score (LP-IPS) has been developed, with one point each for age ≥45 years, stages III-IV, hemoglobin <10.5 g/dL, and splenic involvement.[36] An increasing LP-IPS was significantly associated with a worse progression-free survival (PFS; HR, 1.52) and overall survival (OS; HR, 2.31) and increased risk of lymphoma-specific death (HR, 2.63) and transformation to an aggressive lymphoma histology (HR, 1.41).

4 | RISK-ADAPTED INITIAL THERAPY

The predominant factors that determine the initial choice of therapy for HL patients are the histology of the disease (classical HL or nodular lymphocyte predominant HL), the anatomical stage of disease (limited or advanced disease), the presence of poor prognostic features, the presence of constitutional symptoms and the presence of bulky disease defined as a single site of disease >10 cm in diameter. During treatment, FDG-PET scanning has played a prominent role in decisions to complete therapy as planned, or to add or omit components of treatment. A negative interim FDG-PET may allow to de-escalation of therapy by abbreviating the number of cycles given, omitting radiation therapy, or excluding bleomycin from the treatment to avoid pulmonary toxicity.[37–39] A positive interim FDG-PET scan after 2 cycles of treatment may result in intensification of therapy and a positive PET scan at the end of treatment may result in the addition of consolidation radiotherapy to the positive sites.[33,38,39] A positive PET scan at any point may also result in a repeat biopsy to confirm or exclude persistent disease.[40] The use of PET scans in this fashion is based on the studies showing that patients with a positive FDG-PET scan at the completion of treatment have a significantly higher recurrence rate regardless of the findings on CT scan.[31,41] Also, a FDG-PET done early in the course of treatment (after 2 cycles) predicted PFS and OS for patients with HL and was a better predictor of outcome than stage, extranodal disease or other prognostic factors.[42,43] However, recent clinical trials that have included brentuximab vedotin or immune checkpoint inhibitors in frontline combinations, particularly in patients with advanced disease, have mostly focused on the end of therapy FDG-PET scan results and have not used interim FDG-PET scan results to modify treatment.

4.1 | Initial therapy

The current standard of care for the treatment of patients with HL is to utilize different treatment approaches for patients with early-stage

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disease and favorable prognostic features, those with early-stage disease but who have unfavorable prognostic features, and those with advanced disease. As a general rule, patients with early-stage disease are treated with combined modality strategies utilizing abbreviated courses of combination chemotherapy followed by involved-field radiation therapy (IFRT) in most cases, while those with advanced stage disease receive a longer course of chemotherapy without radiation therapy. However, newer agents including brentuximab vedotin and anti-PD-1 antibodies are now being included in standard combination therapy allowing IFRT to be omitted in early-stage disease and chemotherapy doses to be de-escalated in advanced disease.

4.1.1 | Early-stage favorable HL

Treatment strategies for early-stage HL (stages I-IIA) have changed significantly in the last few decades. Initially, extended field radiation was considered the standard therapy. However, due to the recognition of high relapse rates with significant long-term complications, extended field radiation therapy to involve adjacent lymph node areas is no longer used.[44] A randomized comparison of patients treated with subtotal nodal radiation therapy with or without ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine) and those who received ABVD alone found that patients who received subtotal nodal radiation therapy had a poorer overall survival and a higher rate of death from causes other than Hodgkin lymphoma.[45] Therefore, for favorable early stage disease, short duration chemotherapy for control of occult lesions combined with IFRT restricted only to involved lymph node areas is currently standard practice. Most groups will give 2–4 cycles of combination chemotherapy followed by IFRT to a dose of ~20–35 Gy.[46] This approach is based on the data from a four arm study that randomized early stage HL patients with favorable prognostic factors to either 2 or 4 cycles of ABVD chemotherapy and 20 or 30Gy IFRT. There was no difference between the 4 groups as regards response to therapy, PFS and OS. ABVD for 2 cycles followed by 20Gy IFRT is therefore currently the standard treatment for early-stage favorable prognosis (no adverse risk features) Hodgkin lymphoma.[47]

4.1.2 | Early-stage unfavorable HL

It is generally accepted that patients with stage I and II disease who present with adverse risk factors should be treated with chemotherapy in combination with radiation therapy. However, the optimal number of chemotherapy cycles as well as the optimal chemotherapy regimen; and the dose of radiation as well as the field sizes, are the subject of ongoing studies and debate. This group of patients usually consists of those with bulky mediastinal masses or those with extranodal disease. In these patients, the use of four cycles of combination chemotherapy with IFRT is generally accepted as the treatment of choice.[48,49] This is based on a large clinical trial of stage I/IIA HL patients with unfavorable features who were randomized to ABVD for 4 cycles or baseline doses of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) for 4 cycles plus either 20Gy or 30Gy IFRT. The study found that freedom from treatment failure was worse if 20Gy rather than 30Gy was used with ABVD; however, similar outcomes were seen between 20Gy and 30Gy when used with BEACOPP. The conclusion was that ABVD for 4 cycles plus 30Gy IFRT is the standard for these patients.[49] A subsequent study looked at intensifying the chemotherapy used in this patient group. In this trial, patients with early-stage unfavorable HL received ABVD for 4 cycles or escalated doses of BEACOPP for 2 plus ABVD for 2 cycles. All patients got 30Gy IFRT. The freedom from treatment failure favored the aggressive chemotherapy arm—with a difference of 5.6% at 10 years—but there was no difference in overall survival.[50] There were no differences in treatment-related mortality or secondary malignancies.

Subsequent studies have therefore been developed to determine whether including novel agents such as brentuximab vedotin and PD-1 blocking antibodies can maintain efficacy and decrease potential toxicities in these patients.[51–55] The novel agents have either been given first, concomitantly or as consolidation. The results from these trials have shown that these combination strategies are safe and provide excellent disease control, and these novel combinations are now being compared with the standard approaches (see Table 1). For example, the recent randomized phase II BREACH study compared the efficacy of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (BV-AVD) to standard ABVD followed by 30 Gy involved node radiotherapy (INRT) in previously untreated, early-stage unfavorable Hodgkin lymphoma.[55] The primary endpoint of this 170 patient study was the percent of patients who were FDG-PET negative after two cycles. The primary endpoint of the study was met in that 82.3% of the patients in the BV-AVD arm were PET-negative compared with 75.4% in the ABVD arm. The 2-year PFS was 97.3% and 92.6% in the BV-AVD and ABVD arms, respectively. Similarly, the randomized phase II NIVAHL trial added nivolumab either sequentially or concomitantly to 4 cycles of doxorubicin, vinblastine, and dacarbazine followed by 30 Gy involved-site radiotherapy and found that the PFS at 41 months was 98% and 100% in the sequential and concomitant treatment groups, respectively.[52] These studies show that both brentuximab vedotin and immune checkpoint inhibitors can be safely added to standard therapy for early-stage unfavorable HL patients with excellent results.

4.1.3 | Response-adapted treatment

To further determine the optimal amount of treatment needed, multiple studies have tested functional imaging to provide an early indication of chemosensitivity in HL. FDG-PET has predominantly been used as an interim read-out of efficacy and its utility has been enhanced by the development of a highly reproducible 5-point scale for reporting results.[56] This approach allows for the detection of residual active lymphoma when compared with conventional computed tomography.[43] Results from two large studies illustrate the use

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TABLE 1 Select randomized clinical trial results incorporating targeted therapies into first line therapy for Hodgkin lymphoma.

	Treatment arms	Pts	CR	PFS
Limited stage				
NIVAHL[52] (randomized phase 2)	Concomitant N-AVD ×4 + 30Gy ISRT versus sequential N-AVD ×4 + 30Gy ISRT	109	90% versus 94%	3-yr PFS – 100% versus 98%
BREACH[55] (randomized phase 2)	BV-AVD ×4 + 30Gy INRT versus ABVD ×4 + 30Gy INRT	170	82.3% versus 75.4%	2-yr PFS – 97.3% versus 92.6%
Advanced stage				
ECHELON-1[79] (phase 3)	BV-AVD ×6 versus ABVD ×6	1334	73% versus 71%	6-yr PFS – 82.3% versus 74.5%
HD21[81] (phase 3)	BrECADD ×4–6 versus esc BEACOPP ×4–6 (PET directed)	1500	82% versus 80%	4-yr PFS – 94.3% versus 90.9%
SWOG S1826[84] (phase 3)	N-AVD ×6 versus BV-AVD ×6	994	Not reported	1-yr PFS – 94% versus 86%

Abbreviations: ABVD, doxorubicin, bleomycin, vincristine, and dacarbazine; BV-AVD, brentuximab vedotin, doxorubicin, vincristine, and dacarbazine; CR, complete response; INRT, involved node radiotherapy; ISRT, involved site radiotherapy; N-AVD, nivolumab, doxorubicin, vincristine, and dacarbazine; PET, positron emission tomography; PFS, progression-free survival; Pts, patients; SWOG, Southwest Oncology Group; yr, year.

of a PET-directed approach to either increase or decrease treatment intensity based on initial response to therapy. The United Kingdom National Cancer Research Institute RAPID study randomized patients with non-bulky early stage disease who had a negative interim PET (score of 1 or 2) after 3 cycles of ABVD to either 30 Gy IFRT or no further therapy and found that the 3-year PFS and overall survival were not significantly different between the two arms.[37] However, there was however a trend toward inferior disease control in patients who did not receive radiotherapy, and the difference became statistically significant when patients who did not receive treatment as per protocol were excluded (97.1% vs. 90.8%).

Similarly, the EORTC/ LYSA/FIL H10 study compared standard treatment with ABVD and INRT, to a non-radiotherapy approach using further chemotherapy, for patients with negative FDG-PET scans after 2 cycles of ABVD. An escalation strategy was adopted if patients were PET-positive.[38] In this study, PET-positive patients were switched to two cycles of escalated BEACOPP and INRT, whereas PET-negative patients with both favorable and unfavorable prognostic factors received either ABVD followed by INRT or ABVD only. With long term follow up, in the favorable PET-negative group, the 10-year PFS rates were 98.8% versus 85.4% (p-value for noninferiority = .9735; difference test $p < .0001$) in favor of ABVD + INRT, and in the unfavorable PET-negative group, the 10-year PFS rates were 91.4% and 86.5% (p-value for noninferiority = .8577; difference test $p = .1628$). In PET-positive patients, the difference in terms of PFS between standard ABVD and intensified escalated BEACOPP was not statistically significant ($p = .1777$). The authors concluded that in PET-negative patients, the omission of INRT is associated with lower 10-year PFS,[57] and in PET-positive patients, there was no significant difference between standard therapy and intensified treatment.[58]

In the case of bulky stage I/II disease, patients are typically treated with chemotherapy followed by radiation. A similar PET-adapted approach has also been tested in patients with bulky disease by omitting radiotherapy in patients with interim PET-negative disease and escalating to BEACOPP with 30.6 Gy involved-field radiation in patients with PET-positive disease. In a cohort of 94 patients, the 3-year PFS was 93.1% in PET-negative patients and 89.7% in PET-positive patients, with the majority of patients being spared radiotherapy and exposure to intensified chemotherapy.[59]

The evidence therefore suggests that the use of combined modality treatment produces excellent disease control in patients with early-stage HL, and that a higher percentage of patients may be cured with combined modality therapy. However, approximately 90% of patients, particularly those who are PET-negative after 2–3 cycles of treatment, will be cured with chemotherapy alone. The number needed to treat with radiation to achieve one extra cure is therefore between 15 and 30 based on these studies. Given these excellent results and the potential late toxicity from radiotherapy, many patients may prefer the slightly higher risk of recurrent Hodgkin lymphoma if radiotherapy is omitted, to the potential for long-term complications if radiotherapy is given. In general, however, the outcomes with both approaches are excellent, and the small reduction in disease control does not appear to have a detrimental effect on overall survival. However, a recent real-world study concluded that although the results seen in these clinical trials can replicated in certain patient subgroups, other subgroups particularly those not fitting the trial criteria, do poorly when radiotherapy is excluded.[60]

4.1.4 | Advanced disease

In patients with advanced disease (stages IIB-IV), the challenge is to increase the number of patients with durable remissions while decreasing the likelihood of long-term side effects. A longstanding debate has been whether to use modest chemotherapy, like the ABVD regimen,[61–68] that is reasonably well tolerated with fewer long-term toxicities but a higher rate of inadequate response and relapse, or use more intensive chemotherapy, like escalated BEACOPP, with higher response rates and superior PFS,[69–76] but more toxicity and a greater number of long-term complications.

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To improve clinical outcomes, studies have utilized FDG-PET scans to identify patients who may benefit from intensification or de-escalation of therapy. The AHL2011 and RATHL studies are illustrative of this approach.[33,39] In the AHL2011 study, patients were prospectively randomized between 6 cycles of BEACOPP and a PET-driven arm after 2 cycles of BEACOPP delivering 4 cycles of ABVD in PET2 negative patients and 4 cycles of BEACOPP in PET2 positive patients. With long-term follow up, the PFS and OS were similar in both arms.[33] In the RATHL trial, patients received 2 cycles of ABVD followed by an interim PET scan. Patients with a negative scan were randomized to ABVD or AVD (without bleomycin) for 4 more cycles. Patients with a positive PET scan proceeded to intensification of therapy with either BEACOPP-14 or escalated BEACOPP. In patients with a negative interim PET scan, the 7-year PFS rate and OS rate in the ABVD group and AVD group were similar. The conclusion from this arm of the study was that the omission of bleomycin from the ABVD regimen after a negative interim PET scan did not lower efficacy. In patients with a positive interim PET scan, escalation with BEACOPP was effective and safe, with no increase in second malignancies.[39]

To potentially further improve the outcome of advanced HL patients with poor prognostic features, the role of high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) has been evaluated as part of initial therapy. Patients with advanced unfavorable HL achieving a complete or partial remission after four courses of doxorubicin-containing regimens were found to have a favorable outcome with conventional chemotherapy and no additional benefit from an early intensification with HDCT and ASCT was shown.[77]

The strategies discussed above have largely focused on intensification of therapy to improve the outcome of patients with advanced stage Hodgkin lymphoma. A more recent approach has been to add novel agents including brentuximab vedotin and PD-1 blocking antibodies to standard chemotherapy regimens (see Table 1). Brentuximab vedotin was initially combined with ABVD, and subsequently substituted for bleomycin, in a phase I study.[78] In this combination study, complete responses were seen in most patients. However, significant pulmonary toxicity was seen when brentuximab vedotin was administered in combination with bleomycin resulting in the concurrent use of bleomycin and brentuximab vedotin being contraindicated. Based on the very high response rate, and the fact that brentuximab vedotin was well tolerated when given with AVD chemotherapy, a randomized phase III trial comparing ABVD and AVD plus brentuximab vedotin was completed.[79] The combination of brentuximab vedotin plus AVD had a superior PFS and subsequently OS when compared with ABVD. Neutropenia, requiring growth factor support, and peripheral neuropathy were more common in the brentuximab vedotin plus AVD arm, while pulmonary toxicity was more frequently seen with ABVD. The improvement in OS confirmed that brentuximab vedotin plus AVD is now a preferred frontline option for patients with advanced-stage Hodgkin lymphoma.

The GHSG also explored the use of brentuximab in combination with BEACOPP and developed two new regimens, namely a more conservative variant BrECAPP (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, procarbazine, prednisone) and a more aggressive variant BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone). The results of a randomized phase II trial suggest that use of these combinations, which incorporate an anti-CD30 targeted approach, is feasible without compromising the efficacy associated with escalated BEACOPP.[80] The BrECADD regimen was chosen to be compared to escalated BEACOPP in the randomized GHSG HD21 study.[81] The study enrolled 1500 patients and showed that BrECADD was better tolerated and more effective than eBEACOPP as first-line treatment of adult patients with advanced-stage HL (hazard ratio 0.66; $p = .035$). At a median follow-up of 48 months, the 4-year PFS estimates were 94·3% for BrECADD and 90·9% for eBEACOPP and the 4-year overall survival rates were 98·6% and 98·2%, respectively.

Recent clinical trials have also added anti-PD1 antibodies to AVD chemotherapy (bleomycin omitted) in the frontline setting for patients with newly diagnosed, untreated HL. These studies have first used the PD-1 antibodies alone for 2–3 cycles followed by the subsequent administration or addition of chemotherapy.[54,82] Both studies demonstrated high complete response rates and the progression-free survival suggested promising activity of the combination of immune checkpoint blockade and chemotherapy. Similar results were seen when pembrolizumab was added to AVD chemotherapy.[83] These combinations were well tolerated, and led to a randomized trial comparing brentuximab vedotin plus AVD (BV-AVD) chemotherapy to nivolumab plus AVD (N-AVD) chemotherapy for newly diagnosed patients with advanced stage HL.[84] The initial results of this study was recently reported and with a median follow up of 12.1 months, the PFS was superior in the N-AVD arm (HR 0.48, $p = .0005$)—94% compared to 86%.

Elderly patients constitute a uniquely challenging cHL population as they typically do not tolerate more intense regimens very well. Brentuximab vedotin and PD-1 blocking antibodies are now being used in elderly, either individually in combination with more tolerable chemotherapy regimens or together without the addition of chemotherapy. In a study of patients 60 years or older, patients with advanced stage cHL first received 2 cycles of brentuximab vedotin alone, then 6 cycles of AVD chemotherapy, followed by 4 cycles of brentuximab vedotin.[85] The regimen was well tolerated and the 2-year event-free survival, PFS, and OS rates were excellent for a cohort of elderly patients. Brentuximab vedotin has also been combined with nivolumab, without any chemotherapy, in elderly patients.[86,87] While the response rates in patients receiving this therapy have been promising, the durability of benefit has been modest with many patients having disease progression, particularly if treatment was given for a defined period.[86] In patients >60 years who were able to tolerate either brentuximab vedotin or nivolumab added to AVD chemotherapy, a subgroup analysis of S1826 showed that N-AVD improved PFS and was better tolerated than BV-AVD.[88] These results suggest that incorporating novel agents into frontline therapy may be beneficial for elderly patients but additional trials are needed to optimize the dose and schedule of treatment particularly for frail patients.

In summary, the management of advanced stage HL has changed substantially as the addition of both brentuximab vedotin and

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nivolumab to standard chemotherapy has improved patient outcomes. Currently, N-AVD chemotherapy is the standard of care if a less intense regimen is preferred in lower risk patients and also in elderly patients. If a more dose-intense regimen is considered in patients with multiple poor prognostic factors, BrECADD is the standard of care. However, a randomized trial will be needed to determine whether N-AVD or BrECADD is the preferred regimen for all patients with advanced disease.

4.1.5 | Nodular lymphocyte predominant Hodgkin lymphoma

An exception to the management approach outlined above are patients with early-stage nodular lymphocyte predominant HL. Patients with favorable stage IA disease, with no significant risk factors, can commonly be managed with lymph node excision followed by a 'watch and wait' approach or with IFRT to a dose of ~20–30 Gy.[89] More advanced stage patients with nodular lymphocyte predominant HL are commonly treated with combination chemotherapy, often in combination with rituximab because the malignant cells express CD20.[90] Clinical trials are in progress to define the optimal therapy for this disease.

4.2 | Management of relapsed/refractory disease

Despite the high cure rate with initial therapy, ~5%–10% of HL patients are refractory to initial treatment and 10%–30% of patients will relapse after achieving an initial complete remission.[91] HDCT followed by an ASCT is the standard of care for many patients who relapse following a response to initial chemotherapy.

4.2.1 | Primary refractory disease

Patients with primary refractory disease, defined as progression or non-response during induction treatment or within 90 days of completing treatment, generally have an inferior clinical course. Second-line chemotherapy alone for these patients produces low response rates, with long-term disease-free survival in only 5%–10% of patients.[92,93] Therefore, in these patients, high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is currently considered to be the treatment of choice. A number of retrospective analyses have suggested that patients treated with ASCT have a superior long term outcome when compared with patients treated with chemotherapy.[94,95] An analysis of outcome in primary progressive patients receiving chemotherapy only showed an inferior freedom from failure and overall survival when compared with patients treated with HDCT and an ASCT.[96] Additional studies have confirmed that patients receiving HDCT followed by ASCT have a better outcome than patients treated with chemotherapy.[97,98] However, a substantial proportion of these patients still relapse following HDCT and ASCT.

4.2.2 | Relapsed disease

Between 10% and 30% of patients will relapse following an initial chemotherapy regimen. Patients with progressive disease have typically been treated with salvage chemotherapy regimens similar to what has been used in patients with non-Hodgkin lymphoma. Most eligible patients have then proceeded to undergo an ASCT. However, no randomized trials have been done comparing the effectiveness of different conventional salvage chemotherapeutic regimens, and no optimal salvage regimen has been identified. While treatments with most salvage regimens result in high overall response rates, the goal of salvage therapy is to increase the number of patients achieving a complete response. Recent studies have therefore evaluated whether the addition of brentuximab vedotin or anti-PD-1 antibodies to salvage chemotherapy may improve the complete response rates and increase the number of patients who subsequently receive an ASCT. The combinations of bendamustine plus brentuximab vedotin, brentuximab vedotin plus nivolumab, brentuximab vedotin plus ICE (ifosfamide, carboplatin, etoposide), brentuximab vedotin plus DHAP (dexamethasone, high-dose cytarabine, cisplatin), pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin (GVD), and nivolumab or pembrolizumab plus ICE have resulted in a high complete response rates and successful bridging of most patients to ASCT, some without the need for chemotherapy.[99–105] Recently, a newer PD-1 inhibitor, tislelizumab, was combined with gemcitabine and oxaliplatin with promising results.[106]

Despite the responses seen with salvage therapy, this treatment alone is insufficient treatment, and patients commonly relapse and subsequently die of disease progression if no consolidation is given. A consolidation approach that typically includes HDCT and an ASCT is therefore needed for patients to have durable benefit. Furthermore, a recent multicenter study suggested that salvage combinations that include PD-1 blockade before autologous stem cell transplantation improve outcomes in relapsed and refractory patients.[107] Initial phase II studies suggested that HDCT followed by ASCT may produce a better long-term disease-free survival than expected with conventional chemotherapy in 30%–65% of patients.[108,109] Two subsequent randomized studies confirmed an improved outcome in patients with relapsed HL treated with HDCT followed by ASCT when compared with conventional salvage chemotherapeutic regimens.[110,111] In both studies, the event-free survival after 3 years of patients treated with HDCT was over 50%.

Not all patients are eligible for, or may benefit from, an ASCT. Elderly patients treated with an ASCT have increased treatment-related mortality and commonly have an inferior event-free survival when compared with younger patients.[112] Some patients have relentlessly progressive disease and have been treated with tandem autologous stem-cell transplantation[113] or allogeneic transplantation including haploidentical transplants.[114,115] The data suggested that these therapies are feasible, but toxicity and relapses are common.

To potentially prevent or delay progression post-transplant, particularly in patients with unfavorable risk factors, a randomized, placebo-controlled phase 3 trial of brentuximab vedotin was reported.[116] In this study, patients were randomized to consolidation

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treatment with brentuximab vedotin compared with placebo post autologous stem cell transplant. The median PFS was significantly improved in the brentuximab vedotin treated patients compared with the placebo arm, confirming a benefit for brentuximab vedotin therapy post-transplant in high-risk patients. A far smaller study evaluated the use of pembrolizumab given as consolidation post-transplant in a similar cohort of patients.[117] The primary endpoint was that pembrolizumab would improve the progression-free survival at 18 months after ASCT and the study met its primary end point. However, this potential benefit of immune checkpoint blockade post-ASCT will need to be confirmed in a randomized trial.

4.2.3 | Therapeutic options following relapse after HDCT and ASCT

Patients with progression of disease after ASCT historically had a poor outcome.[118] However, the outcome of patients with Hodgkin lymphoma who relapse after autologous stem cell transplant has improved in recent years.[119] The improved outcome is in large part due to the use of novel agents including antibody drug conjugates and PD-1 blocking antibodies.

Brentuximab vedotin, an antibody drug conjugate targeting CD30, is an established therapy particularly in HL patients who have relapsed post-transplant. The initial studies testing this agent were conducted in the post-transplant patient population and the showed significant clinical activity. In the pivotal phase II trial of brentuximab vedotin in HL patients who had failed an ASCT, clinical responses was seen in three quarters of patients and a third of the patients had a CR.[120] Similarly, treatment with antibodies that block the interaction between PD-1 and PD-L1 or PD-L2 also result in very high clinical response rates in this patient population.[121–126] The efficacy of PD-1 blockade, using pembrolizumab, was recently compared in a randomized trial to the efficacy of brentuximab vedotin for relapsed or refractory classical Hodgkin lymphoma. Pembrolizumab treatment showed a significant improvement in PFS compared with treatment with brentuximab vedotin supporting PD-1 blockade as the preferred first treatment option for patients who relapse post-autologous ASCT or are ineligible for an autologous HSCT.[127]

Other promising approaches in this patient population include combination strategies, chimeric antigen receptor (CAR) T-cell therapy, and new antibody drug conjugates. Brentuximab vedotin has been combined with two checkpoint inhibitors, nivolumab and ipilimumab, and the efficacy of the triplet combination was very promising.[128] CAR T-cell therapy is still early in development but has been shown to be safe with very promising clinical activity.[129,130] Finally, the innate cell engager AFM13 is a first-in-class CD30/CD16A bispecific antibody construct that induces selective killing of CD30+ tumor cells by engaging and activating NK cells. When AFM13 was combined with preactivated cord blood derived NK cells and administered to patients with CD30+ lymphomas (37 of 42 patients had HL), the ORR and CR rates were 92.8% and 66.7%, respectively suggesting that this could be a promising future therapy for relapsed patients.[131]

5 | SUMMARY

Optimal management of patients with HL requires an accurate diagnosis and careful staging of the disease. Identification of poor prognostic features then allows for risk-adapted therapy to potentially increase the likelihood of cure and limit toxicity. Future directions to further improve the outcome of patients with HL will incorporate additional novel agents into treatment combinations to increase efficacy and will utilize novel imaging and peripheral blood molecular assays to minimize the amount of treatment needed to cure patients with this disease.

CONFLICT OF INTEREST STATEMENT

The author receives research funding paid to his institution for clinical trials from Bristol Myers Squibb, Takeda, Pfizer, AstraZeneca, Affimed, Regeneron and ADC Therapeutics.

DATA AVAILABILITY STATEMENT

All data is publically available in the medical literature.

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REFERENCES

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49.
2. Glaser SL, Jarrett RF. The epidemiology of Hodgkin's disease. *Baillieres Clin Haematol*. 1996;9(3):401-416.
3. Zhou L, Deng Y, Li N, et al. Global, regional, and national burden of Hodgkin lymphoma from 1990 to 2017: estimates from the 2017 global burden of disease study. *J Hematol Oncol*. 2019;12(1):107.
4. Hemminki K, Sundquist K, Sundquist J, Försti A, Hemminki A, Li X. Familial risks and proportions describing population landscape of familial cancer. *Cancers (Basel)*. 2021;13(17):4385.
5. Grufferman S, Cole P, Smith PG, Lukes RJ. Hodgkin's disease in siblings. *N Engl J Med*. 1977;296(5):248-250.
6. Lynch HT, Marcus JN, Lynch JF. Genetics of Hodgkin's and non-Hodgkin's lymphoma: a review. *Cancer Invest*. 1992;10(3):247-256.
7. Flerlage JE, Myers JR, Maciaszek JL, et al. Discovery of novel predisposing coding and noncoding variants in familial Hodgkin lymphoma. *Blood*. 2023;141(11):1293-1307.
8. Horwitz M, Wiernik PH. Pseudoautosomal linkage of Hodgkin disease. *Am J Hum Genet*. 1999;65(5):1413-1422.
9. Mack TM, Cozen W, Shibata DK, et al. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. *N Engl J Med*. 1995;332(7):413-418.
10. Weiss LM, Strickler JG, Warnke RA, Purtilo DT, Sklar J. Epstein-Barr viral DNA in tissues of Hodgkin's disease. *Am J Pathol*. 1987;129(1):86-91.
11. Alexander FE, Jarrett RF, Lawrence D, et al. Risk factors for Hodgkin's disease by Epstein-Barr virus (EBV) status: prior infection by EBV and other agents. *Br J Cancer*. 2000;82(5):1117-1121.
12. Franceschi S, Dal Maso L, La Vecchia C. Advances in the epidemiology of HIV-associated non-Hodgkin's lymphoma and other lymphoid neoplasms. *Int J Cancer*. 1999;83(4):481-485.
13. Andrieu JM, Roithmann S, Tourani JM, et al. Hodgkin's disease during HIV1 infection: the French registry experience. French registry of HIV-associated tumors. *Ann Oncol*. 1993;4(8):635-641.

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14. Tirelli U, Errante D, Dolcetti R, et al. Hodgkin's disease and human immunodeficiency virus infection: clinicopathologic and virologic features of 114 patients from the Italian cooperative group on AIDS and tumors. *J Clin Oncol*. 1995;13(7):1758-1767.
15. Stein H, Delsol G, Pileri SA. Hodgkin lymphoma. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. *WHO Classification of Tumours; Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Vol 3. 3rd ed. IARC Press; 2001:237-253.
16. Marafioti T, Hummel M, Foss HD, et al. Hodgkin and reed-sternberg cells represent an expansion of a single clone originating from a germinal center B-cell with functional immunoglobulin gene rearrangements but defective immunoglobulin transcription. *Blood*. 2000;95(4):1443-1450.
17. Kanzler H, Kuppers R, Hansmann ML, Rajewsky K. Hodgkin and reed-Sternberg cells in Hodgkin's disease represent the outgrowth of a dominant tumor clone derived from (crippled) germinal center B cells. *J Exp Med*. 1996;184(4):1495-1505.
18. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of Haematolymphoid Tumours: lymphoid neoplasms. *Leukemia*. 2022 Jul;36(7):1720-1748.
19. Fan Z, Natkunam Y, Bair E, Tibshirani R, Warnke RA. Characterization of variant patterns of nodular lymphocyte predominant hodgkin lymphoma with immunohistologic and clinical correlation. *Am J Surg Pathol*. 2003;27:1346-1356.
20. Campo E, Jaffe ES, Cook JR, et al. The international consensus classification of mature lymphoid neoplasms: a report from the clinical advisory committee. *Blood*. 2022;140(11):1229-1253.
21. Ekstrand BC, Horning SJ. Hodgkin's disease. *Blood Rev*. 2002;16(2):111-117.
22. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116(17):3268-3277.
23. Roemer MG, Advani RH, Ligon AH, et al. PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome. *J Clin Oncol*. 2016;34(23):2690-2697.
24. Alig SK, Shahrokh Esfahani M, Garofalo A, et al. Distinct Hodgkin lymphoma subtypes defined by noninvasive genomic profiling. *Nature*. 2024;625(7996):778-787.
25. Pinkus GS, Said JW. Hodgkin's disease, lymphocyte predominance type, nodular–further evidence for a B cell derivation. L & H variants of reed-Sternberg cells express L26, a pan B cell marker. *Am J Pathol*. 1988;133(2):211-217.
26. Diehl V, Sextro M, Franklin J, et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European task force on lymphoma project on lymphocyte-predominant Hodgkin's disease. *J Clin Oncol*. 1999;17(3):776-783.
27. Jerusalem G, Beguin Y, Fassotte MF, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose compared to standard procedures for staging patients with Hodgkin's disease. *Haematologica*. 2001;86(3):266-273.
28. Barrington SF, Kirkwood AA, Franceschetto A, et al. PET-CT for staging and early response: results from the response-adapted therapy in advanced Hodgkin lymphoma study. *Blood*. 2016;127(12):1531-1538.
29. Diehl V, Stein H, Hummel M, Zollinger R, Connors JM. Hodgkin's lymphoma: biology and treatment strategies for primary, refractory, and relapsed disease. *Hematology Am Soc Hematol Educ Program*. 2003;2003:225-247.
30. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced Hodgkin's disease. *N Engl J Med*. 1998;339(21):1506-1514.
31. Jerusalem G, Beguin Y, Fassotte MF, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood*. 1999;94(2):429-433.
32. Barrington SF, Phillips EH, Counsell N, et al. Positron emission tomography score has greater prognostic significance than pretreatment risk stratification in early-stage Hodgkin lymphoma in the UK RAPID study. *J Clin Oncol*. 2019;37(20):1732-1741.
33. Casasnovas RO, Bouabdallah R, Brice P, et al. Positron emission tomography-driven strategy in advanced Hodgkin lymphoma: prolonged follow-up of the AHL2011 phase III lymphoma study association study. *J Clin Oncol*. 2022;40(10):1091-1101.
34. Cottereau AS, Versari A, Loft A, et al. Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. *Blood*. 2018;131(13):1456-1463.
35. Mettler J, Müller H, Voltin CA, et al. Metabolic tumour volume for response prediction in advanced-stage Hodgkin lymphoma. *J Nucl Med*. 2018;60(2):207-211.
36. Binkley MS, Flerlage JE, Savage KJ, et al. International prognostic score for nodular lymphocyte-predominant Hodgkin lymphoma. *J Clin Oncol*. 2024;42(19):2271-2280.
37. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med*. 2015;372(17):1598-1607.
38. André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2017;35(16):1786-1794.
39. Luminari S, Fossa A, Trotman J, et al. Long-term follow-up of the response-adjusted therapy for advanced Hodgkin lymphoma trial. *J Clin Oncol*. 2024;42(1):13-18.
40. Novo M, Nowakowski GS, Habermann TM, et al. Persistent mediastinal FDG uptake on PET-CT after frontline therapy for Hodgkin lymphoma: biopsy, treat or observe? *Leuk Lymphoma*. 2020;61(2):318-327.
41. Zinzani PL, Magagnoli M, Chierichetti F, et al. The role of positron emission tomography (PET) in the management of lymphoma patients. *Ann Oncol*. 1999;10(10):1181-1184.
42. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol*. 2007;25(24):3746-3752.
43. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood*. 2006;107(1):52-59.
44. Brusamolino E, Lazzarino M, Orlandi E, et al. Early-stage Hodgkin's disease: long-term results with radiotherapy alone or combined radiotherapy and chemotherapy. *Ann Oncol*. 1994;5(Suppl 2):101-106.
45. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med*. 2012;366(5):399-408.
46. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol*. 2004;22(14):2835-2841.
47. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363(7):640-652.
48. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of

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the German Hodgkin's lymphoma study group. *J Clin Oncol*. 2003; 21(19):3601-3608.
49. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin study group HD11 trial. *J Clin Oncol*. 2010;28(27):4199-4206.
50. Gillessen S, Plütschow A, Fuchs M, et al. Intensified treatment of patients with early stage, unfavourable Hodgkin lymphoma: long-term follow-up of a randomised, international phase 3 trial of the German Hodgkin study group (GHSG HD14). *Lancet Haematol*. 2021;8(4):e278-e288.
51. Abramson JS, Arnason JE, LaCasce AS, et al. Brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine for nonbulky limited-stage classical Hodgkin lymphoma. *Blood*. 2019;134(7):606-613.
52. Bröckelmann PJ, Bühnen I, Meissner J, et al. Nivolumab and doxorubicin, vinblastine, and dacarbazine in early-stage unfavorable hodgkin lymphoma: final analysis of the randomized German Hodgkin study group phase II NIVAHL trial. *J Clin Oncol*. 2023;41:1193-1199.
53. Park SI, Shea TC, Olajide O, et al. ABVD followed by BV consolidation in risk-stratified patients with limited-stage Hodgkin lymphoma. *Blood Adv*. 2020;4(11):2548-2555.
54. Allen PB, Savas H, Evens AM, et al. Pembrolizumab followed by AVD in untreated early unfavorable and advanced-stage classical Hodgkin lymphoma. *Blood*. 2021;137(10):1318-1326.
55. Fornecker LM, Lazarovici J, Aurer I, et al. Brentuximab Vedotin plus AVD for first-line treatment of early-stage unfavorable Hodgkin lymphoma (BREACH): a multicenter, open-label, randomized, phase II trial. *J Clin Oncol*. 2023;41(2):327-335.
56. Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. *Eur J Nucl Med Mol Imaging*. 2010;37(10):1824-1833.
57. Fiaccadori V, Neven A, Fortpied C, et al. Relapse patterns in early-PET negative, limited-stage Hodgkin lymphoma (HL) after ABVD with or without radiotherapy-a joint analysis of EORTC/LYSA/FIL H10 and NCRI RAPID trials. *Br J Haematol*. 2023;200(6):731-739.
58. Federico M, Fortpied C, Stepanishyna Y, et al. Long-term follow-up of the response-adapted intergroup EORTC/LYSA/FIL H10 trial for localized Hodgkin lymphoma. *J Clin Oncol*. 2024;42:19-25.
59. LaCasce AS, Dockter T, Ruppert AS, et al. Positron emission tomography-adapted therapy in bulky stage I/II classic Hodgkin lymphoma: CALGB 50801 (Alliance). *J Clin Oncol*. 2023;41(5): 1023-1034.
60. Chohan KL, Young JR, Lester S, et al. A real-world study of combined modality therapy for early-stage Hodgkin lymphoma: too little treatment impacts outcome. *Blood Adv*. 2022;6(14):4241-4250.
61. Bonadonna G, Valagussa P, Santoro A. Alternating non-cross-resistant combination chemotherapy or MOPP in stage IV Hodgkin's disease. A report of 8-year results. *Ann Intern Med*. 1986; 104(6):739-746.
62. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med*. 1992;327(21):1478-1484.
63. Viviani S, Bonadonna G, Santoro A, et al. Alternating versus hybrid MOPP and ABVD combinations in advanced Hodgkin's disease: ten-year results. *J Clin Oncol*. 1996;14(5):1421-1430.
64. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *J Clin Oncol*. 2003; 21(4):607-614.
65. Bartlett NL, Rosenberg SA, Hoppe RT, Hancock SL, Horning SJ. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. *J Clin Oncol*. 1995;13(5):1080-1088.
66. Chisesi T, Bellei M, Luminari S, et al. Long-term follow-up analysis of HD9601 trial comparing ABVD versus Stanford V versus MOPP/EBV/CAD in patients with newly diagnosed advanced-stage Hodgkin's lymphoma: a study from the Intergruppo Italiano Linfomi. *J Clin Oncol*. 2011;29(32):4227-4233.
67. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the stanford V regimen and ABVD in the treatment of advanced Hodgkin's lymphoma: United Kingdom National Cancer Research Institute lymphoma group study ISRCTN 64141244. *J Clin Oncol*. 2009;27(32):5390-5396.
68. Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the eastern cooperative oncology group (E2496). *J Clin Oncol*. 2013;31(6):684-691.
69. Diehl V, Sieber M, Ruffer U, et al. BEACOPP: an intensified chemotherapy regimen in advanced Hodgkin's disease. The German Hodgkin's lymphoma study group. *Ann Oncol*. 1997;8(2):143-148.
70. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *J Clin Oncol*. 2009; 27(27):4548-4554.
71. Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo studio dei Linfomi trial. *J Clin Oncol*. 2009; 27(5):805-811.
72. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet*. 2012;379(9828): 1791-1799.
73. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med*. 2011;365(3):203-212.
74. Connors JM. Hodgkin's lymphoma–the great teacher. *N Engl J Med*. 2011;365(3):264-265.
75. Tam CS, Herschtal A, Seymour JF. ABVD versus BEACOPP for Hodgkin's lymphoma. *N Engl J Med*. 2011;365(16):1544-1545. author reply 1546.
76. Skoetz N, Trelle S, Rancea M, et al. Effect of initial treatment strategy on survival of patients with advanced-stage Hodgkin's lymphoma: a systematic review and network meta-analysis. *Lancet Oncol*. 2013;14(10):943-952.
77. Federico M, Bellei M, Brice P, et al. High-dose therapy and autologous stem-cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy. *J Clin Oncol*. 2003;21(12):2320-2325.
78. Younes A, Connors JM, Park SI, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. *Lancet Oncol*. 2013;14(13):1348-1356.
79. Ansell SM, Radford J, Connors JM, et al. Overall survival with Brentuximab Vedotin in stage III or IV Hodgkin's lymphoma. *N Engl J Med*. 2022;387(4):310-320.
80. Damaschin C, Goergen H, Kreissl S, et al. Brentuximab vedotin-containing escalated BEACOPP variants for newly diagnosed advanced-stage classical Hodgkin lymphoma: follow-up analysis of a randomized phase II study from the German Hodgkin study group. *Leukemia*. 2022;36(2):580-582.
81. Borchmann P, Ferdinandus J, Schneider G, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. *Lancet*. 2024; 404(10450):341-352.

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82. Ramchandren R, Domingo-Domenech E, Rueda A, et al. Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the phase II CheckMate 205 study. *J Clin Oncol*. 2019;37(23):1997-2007.
83. Lynch RC, Ujjani CS, Poh C, et al. Concurrent pembrolizumab with AVD for untreated classical Hodgkin lymphoma. *Blood*. 2023;141:2576-2586.
84. Herrera AF, LeBlanc ML, Castellino SM, et al. SWOG S1826, a randomized study of nivolumab (N)-AVD versus brentuximab vedotin (BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). *J Clin Oncol*. 2023;41:LBA4. doi:10.1200/JCO.2023.41.17_suppl.LBA4
85. Evens AM, Advani RH, Helenowski IB, et al. Multicenter phase II study of sequential Brentuximab Vedotin and doxorubicin, vinblastine, and Dacarbazine chemotherapy for older patients with untreated classical Hodgkin lymphoma. *J Clin Oncol*. 2018;36(30):3015-3022.
86. Cheson BD, Bartlett NL, LaPlant B, et al. Brentuximab vedotin plus nivolumab as first-line therapy in older or chemotherapy-ineligible patients with Hodgkin lymphoma (ACCRU): a multicentre, single-arm, phase 2 trial. *Lancet Haematol*. 2020;7(11):e808-e815.
87. Friedberg JW, Bordoni R, Patel-Donnelly D, et al. Brentuximab vedotin with dacarbazine or nivolumab as frontline cHL therapy for older patients ineligible for chemotherapy. *Blood*. 2024;143:786-795.
88. Rutherford SC, Li H, Herrera AF, et al. Nivolumab-AVD is better tolerated and improves progression-free survival compared to Bv-AVD in older patients (aged ≥60 years) with advanced stage Hodgkin lymphoma enrolled on SWOG S1826. *Blood*. 2023;142:181-1181.
89. Binkley MS, Rauf MS, Milgrom SA, et al. Stage I-II nodular lymphocyte-predominant Hodgkin lymphoma: a multi-institutional study of adult patients by ILROG. *Blood*. 2020;135(26):2365-2374.
90. Fanale MA, Cheah CY, Rich A, et al. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. *Blood*. 2017;130(4):472-477.
91. Diehl V, Mauch PM, Harris NL. Hodgkin's disease. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Vol 6. Lippincott Williams & Wilkins; 2001:2239-2386.
92. Longo DL, Duffey PL, Young RC, et al. Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. *J Clin Oncol*. 1992;10(2):210-218.
93. Bonfante V, Santoro A, Viviani S, et al. Outcome of patients with Hodgkin's disease failing after primary MOPP-ABVD. *J Clin Oncol*. 1997;15(2):528-534.
94. Ferme C, Mounier N, Divine M, et al. Intensive salvage therapy with high-dose chemotherapy for patients with advanced Hodgkin's disease in relapse or failure after initial chemotherapy: results of the Groupe d'Etudes des Lymphomes de l'Adulte H89 trial. *J Clin Oncol*. 2002;20(2):467-475.
95. Josting A, Rueffer U, Franklin J, Sieber M, Diehl V, Engert A. Prognostic factors and treatment outcome in primary progressive Hodgkin lymphoma: a report from the German Hodgkin lymphoma study group. *Blood*. 2000;96(4):1280-1286.
96. Andre M, Henry-Amar M, Pico JL, et al. Comparison of high-dose therapy and autologous stem-cell transplantation with conventional therapy for Hodgkin's disease induction failure: a case-control study. Societe Francaise de Greffe de Moelle. *J Clin Oncol*. 1999;17(1):222-229.
97. Reece DE, Barnett MJ, Shepherd JD, et al. High-dose cyclophosphamide, carmustine (BCNU), and etoposide (VP16-213) with or without cisplatin (CBV +/− P) and autologous transplantation for patients with Hodgkin's disease who fail to enter a complete remission after combination chemotherapy. *Blood*. 1995;86(2):451-456.
98. Lazarus HM, Rowlings PA, Zhang MJ, et al. Autotransplants for Hodgkin's disease in patients never achieving remission: a report from the autologous blood and marrow transplant registry. *J Clin Oncol*. 1999;17(2):534-545.
99. Moskowitz AJ, Schoder H, Yahalom J, et al. PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study. *Lancet Oncol*. 2015;16(3):284-292.
100. LaCasce AS, Bociek RG, Sawas A, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;132(1):40-48.
101. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;131(11):1183-1194.
102. Kersten MJ, Driessen J, Zijlstra JM, et al. Combining brentuximab vedotin with dexamethasone, high-dose cytarabine and cisplatin as salvage treatment in relapsed or refractory Hodgkin lymphoma: the phase II HOVON/LLPC transplant BRaVE study. *Haematologica*. 2021;106(4):1129-1137.
103. Moskowitz AJ, Shah G, Schöder H, et al. Phase II trial of Pembrolizumab plus gemcitabine, Vinorelbine, and liposomal doxorubicin as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. *J Clin Oncol*. 2021;39(28):3109-3117.
104. Mei MG, Lee HJ, Palmer JM, et al. Response-adapted anti-PD-1-based salvage therapy for Hodgkin lymphoma with nivolumab alone or in combination with ICE. *Blood*. 2022;139(25):3605-3616.
105. Bryan LJ, Casulo C, Allen PB, et al. Pembrolizumab added to ifosfamide, carboplatin, and etoposide chemotherapy for relapsed or refractory classic Hodgkin lymphoma: a multiinstitutional phase 2 investigator-initiated nonrandomized clinical trial. *JAMA Oncol*. 2023;9:683-691.
106. Ding K, Liu H, Ma J, et al. Tislelizumab with gemcitabine and oxaliplatin in patients with relapsed or refractory classic Hodgkin lymphoma: a multicenter phase II trial. *Haematologica*. 2023;108:2146-2154.
107. Desai SH, Merryman RW, Shah H, et al. PD-1 blockade before autologous stem cell transplantation improves outcomes in relapsed/refractory classic hodgkin lymphoma: results from a multicenter cohort. *Blood*. 2023;142:1182.
108. Josting A, Katay I, Rueffer U, et al. Favorable outcome of patients with relapsed or refractory Hodgkin's disease treated with high-dose chemotherapy and stem cell rescue at the time of maximal response to conventional salvage therapy (Dex-BEAM). *Ann Oncol*. 1998;9(3):289-295.
109. Brice P, Bouabdallah R, Moreau P, et al. Prognostic factors for survival after high-dose therapy and autologous stem cell transplantation for patients with relapsing Hodgkin's disease: analysis of 280 patients from the French registry. Societe Francaise de Greffe de Moelle. *Bone Marrow Transplant*. 1997;20(1):21-26.
110. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993;341(8852):1051-1054.
111. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359(9323):2065-2071.
112. Kusnierz-Glaz CR, Schlegel PG, Wong RM, et al. Influence of age on the outcome of 500 autologous bone marrow transplant procedures for hematologic malignancies. *J Clin Oncol*. 1997;15(1):18-25.
113. Brice P, Divine M, Simon D, et al. Feasibility of tandem autologous stem-cell transplantation (ASCT) in induction failure or very

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unfavorable (UF) relapse from Hodgkin's disease (HD). SFGM/GELA Study Group. *Ann Oncol*. 1999;10(12):1485-1488.
114. Ahmed S, Ghosh N, Ahn KW, et al. Impact of type of reduced-intensity conditioning regimen on the outcomes of allogeneic haematopoietic cell transplantation in classical Hodgkin lymphoma. *Br J Haematol*. 2020;190(4):573-582.
115. Castagna L, Busca A, Bramanti S, et al. Haploidentical related donor compared to HLA-identical donor transplantation for chemosensitive Hodgkin lymphoma patients. *BMC Cancer*. 2020;20(1):1140.
116. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015;385(9980):1853-1862.
117. Armand P, Chen YB, Redd RA, et al. PD-1 blockade with pembrolizumab for classical Hodgkin lymphoma after autologous stem cell transplantation. *Blood*. 2019;134(1):22-29.
118. Kewalramani T, Nimer SD, Zelenetz AD, et al. Progressive disease following autologous transplantation in patients with chemosensitive relapsed or primary refractory Hodgkin's disease or aggressive non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 2003;32(7):673-679.
119. Bazarbachi A, Boumendil A, Finel H, et al. The outcome of patients with Hodgkin lymphoma and early relapse after autologous stem cell transplant has improved in recent years. *Leukemia*. 2022;36(6):1646-1653.
120. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30(18):2183-2189.
121. Armand P, Zinzani PL, Lee HJ, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. *Blood*. 2023;142:878-886.
122. Ansell SM, Bröckelmann PJ, von Keudell G, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma: 5-year survival from pivotal phase 2 CheckMate 205 study. *Blood Adv*. 2023;7:6266-6274.
123. Shi Y, Su H, Song Y, et al. Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): a multicentre, single-arm, phase 2 trial. *Lancet Haematol*. 2019;6(1):e12-e19.
124. Song Y, Gao Q, Zhang H, et al. Treatment of relapsed or refractory classical Hodgkin lymphoma with the anti-PD-1, tislelizumab: results of a phase 2, single-arm, multicenter study. *Leukemia*. 2020;34(2):533-542.
125. Wu J, Song Y, Chen X, et al. Camrelizumab for relapsed or refractory classical Hodgkin lymphoma: extended follow-up of the multicenter, single-arm, phase 2 study. *Int J Cancer*. 2022;150(6):984-992.
126. Herrera AF, Burton C, Radford J, et al. Avelumab in relapsed/refractory classical Hodgkin lymphoma: phase 1b results from the JAVELIN Hodgkins trial. *Blood Adv*. 2021;5(17):3387-3396.
127. Kuruvilla J, Ramchandren R, Santoro A, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol*. 2021;22(4):512-524.
128. Diefenbach CS, Hong F, Ambinder RF, et al. Ipilimumab, nivolumab, and brentuximab vedotin combination therapies in patients with relapsed or refractory Hodgkin lymphoma: phase 1 results of an open-label, multicentre, phase 1/2 trial. *Lancet Haematol*. 2020;7(9):e660-e670.
129. Ramos CA, Grover NS, Beaven AW, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol*. 2020;38(32):3794-3804.
130. Wang CM, Wu ZQ, Wang Y, et al. Autologous T cells expressing CD30 chimeric antigen receptors for relapsed or refractory Hodgkin lymphoma: an open-label phase I trial. *Clin Cancer Res*. 2017;23(5):1156-1166.
131. Nieto Y, Banerjee P, Kaur I, et al. Innate cell engager (ICE®) AFM13 combined with Preactivated and expanded (P+E) cord blood (CB)-derived natural killer (NK) cells for patients with refractory CD30-positive lymphomas: final results. *Blood*. 2023;142:774.

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